European College of Neuropsychopharmacology – press release

Study shows alcohol-dependent men and women have different biochemistries, so may need different treatments

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MILAN — A new study reveals hormonal and biochemical factors that affect alcohol dependence (also known as Alcohol Use Disorder), suggesting that men and women with alcohol problems may benefit from different treatments.

Scientists have known that men and women have different risks related to alcohol misuse and related problems and that alcohol treatments may need to be tailored differently to men and women. However, the biological mechanisms underlying those differences are not well understood.

"This is the first large study to confirm that some of the variability in Alcohol Use Disorder (AUD) and related problems is associated with particular combinations of hormones and chemical biomarkers in men and in women. It may mean that sex-specific treatments can be tailored to improve responses for men and women with alcohol problems" said lead researcher Victor Karpyak, Professor of Psychiatry at Mayo Clinic in Rochester, Minnesota (USA). This work is presented at the ECNP Congress in Milan, Italy.

As part of a research project researching the alcohol dependence medication acamprosate, the researchers looked at hormonal and protein markers of 268 men and 132 women with Alcohol Use Disorder. They correlated these markers with psychological markers, such as depressed mood, anxiety, craving, alcohol consumption and treatment outcomes during the first 3 months of treatment.

At the beginning of the trial – before anyone had taken any medication – the researchers tested men and women for several sex-specific blood markers, including sex hormones (testosterone, estrogens, progesterone) as well as proteins known to impact their reproduction (such as follicle stimulating hormone, and luteinizing hormone) or bioavailability of these hormones in the blood (albumin and sex hormone-binding globulin).

They found that at the beginning of the trial men with Alcohol Use Disorder, symptoms of depression, and higher craving for alcohol, also had lower levels of the hormones testosterone, estrone, estradiol, as well as the protein sex hormone binding globulin. No such associations were found in women with AUD.

At the start of the trial, MEN with a high craving for alcohol had:

- Low levels of the hormones testosterone, estrone, estradiol,
- Low levels of the protein sex hormone binding globulin.

At the start of the trial, WOMEN with a high craving for alcohol did not have low levels of these these biochemical changes

Professor Karpyak said, "*We found that there were different associations in men and women. For example, women who had higher levels of testosterone, sex hormone binding globulin, and albumin were also more likely to relapse during the first three months of treatment compared to women with lower levels of those biochemical markers. No such relationships were found in men.*

In first 3 months treatment:

WOMEN with higher levels of testosterone, sex hormone binding globulin, and albumin were more likely to relapse compared to WOMEN with lower levels of those biochemical markers

No such association found in Men

"These hormones and proteins are known to have an influence on behaviour, and indeed we see an association between different levels of these compounds and different behavioural aspects of alcohol use disorder, although we can't for sure say that one directly causes another. What it does mean is that if you are treating a man and a woman for alcoholism, you are dealing with different biochemical and psychological starting points. This implies that what works for a man may not work for a woman, and vice versa.

"This is the first study large enough to be able to confirm that particular combinations of sex hormones and related proteins may be part of the biological differences in how alcoholism manifests itself in men and women. We need more research to understand what this means for disease progression and its treatment. Given that many of those differences are related to sex hormones, we particularly want to see how the dramatic hormonal change women experience during menstrual cycle and at menopause may affect the biochemistry of alcoholism, and guide treatment efforts".

Commenting, Dr Erika Comasco, Associate Professor in Molecular Psychiatry, Uppsala University, Sweden, said," *This research is an important step forward to gender equity in medicine. The findings provide an important first insight into the relationship between sex hormones and alcohol use disorder treatment. While sex differences in the way the disorder manifests itself are known, these results*

suggest that sex hormones may modulate treatment response, potentially supporting sex-specific pharmacological intervention. However, hormone fluctuations related to the menstrual cycle are also potential modulators of alcohol misuse, warranting further investigation into their role in treatment and relapse outcomes for female patients."

This is an independent comment, Professor Comasco was not involved in this work.

Notes

Sex Hormone Binding Globulin (SHBG) and Albumin are proteins made by the liver. SHBG carries the hormones estrogen, dihydrotestosterone (DHT), and testosterone in the bloodstream, whereas albumin helps control fluid in the blood, as well as carrying hormones and some chemicals in the bloodstream (simplified definitions).

Notes for Editors

This work is presented at the 37th ECNP Congress, taking place in Milan and online 21-24 September 2024, see https://www.ecnp.eu/Congress2024/ECNPcongress. With more than 6,500 participants the ECNP Congress is Europe's leading platform for the latest research in disease-related neuroscience.

Conference abstract: P2001

Exploring the relationship between plasma sex-related hormone and protein levels with clinical characteristics and treatment outcomes in alcohol dependent patients

V. Karpyak[1], Y. Song[2], A.M.C. Ho[1], J. Geske[3], V. Pazdernik[3], C. Waller[3], S. Winham[3]

[1]Mayo Clinic, Department of Psychiatry and Psychology, Rochester- MN, United States

[2]University of Washington, Department of Biostatistics, Seattle, United States

[3]Mayo Clinic, Department of Quantitative Health Sciences, Rochester- MN, United States

Introduction

Alcohol Use Disorder (AUD) is marked by persistent alcohol consumption despite negative consequences. Notably, there are discernible sex-based differences in AUD-related phenomenology, including craving, withdrawal, and patterns of consumption, as well as psychiatric comorbidities, including depression and anxiety. Prior research noted variations in plasma levels of steroid sex hormones and their protein regulators among individuals with AUD compared to those without[1,2]. The interplay between hormones and mental health, particularly depression in women, is evident[3,4]. Most studies focused on the links between AUD and sex-related hormones and proteins individually. However, little is understood about their combined effects, which may provide further insights hormone dysregulation in AUD features and treatment outcomes between sexes.

Study Aims

Explore associations between sex-related hormone and protein combinations with (1) baseline measurements, including craving, consumption, depression, and anxiety; and (2) acamprosate treatment outcomes, including relapse and days of sobriety over the initial 3 months.

Methods

About 400 treatment-seeking individuals diagnosed with DSM-IV-TR alcohol dependence were recruited for a clinical trial of acamprosate. AUD and psychiatric comorbidities were verified by Psychiatric Research Interview for Substance and Mental Disorder (PRISM). The intensity of depressed mood, anxiety, craving, and alcohol consumption were measured by Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD-7), Penn Alcohol Craving Scale (PACS), and Timeline Followback (TLFB), respectively. Clinical data and blood samples were collected after detoxification but before the start of the acamprosate regimen (i.e., baseline) as well as at follow-up visits up to 6 months. Sex-related hormones and proteins (testosterone, estrone, estradiol, progesterone, follicle-stimulating hormone [FSH], luteinizing hormone [LH], sex hormone binding globulin [SHBG], and albumin) were measured in baseline plasma samples by mass spectrometry or immunoassays. We first used Principal Component Analysis to obtain 8 independent hormone and protein combinations. Then, linear regressions with robust standard errors, logistic regressions, negative binomial

models, and survival analysis were performed to assess the association between these combinations and various outcomes. We adjusted for age, BMI, and menopause status (for females only).

Results

In AUD males, a combination of lower baseline testosterone, estrone, estradiol, and SHBG was associated with lower baseline PHQ-9 (ß=-0.077, p=0.0102) and PACS scores (ß=-1.071, p=0.0014). A combination of higher baseline progesterone and lower albumin was associated with lower risk of relapse during the first 3 months (OR=0.518, p=0.0079).

In AUD females, a combination of lower estrone, estradiol and higher FSH and LH is associated with higher maximum number of drinks per day (ß=0.076, p=0.035). A combination of higher testosterone, SHBG, and albumin is associated with higher risk of relapse during the first 3 months (OR=4.536, p=0.0057) and higher risk of lifetime depression history (OR=1.545, p=0.048). Moreover, these two hormone profiles were also associated with higher risk of lifetime anxiety history (OR=1.359 and 1.618, p=0.0335 and 0.0307).

Conclusions

Our study identified sex-specific associations of particular hormone/protein profiles with clinical phenomenology and treatment outcome in men and women with AUD. These findings validate the need for further investigation of the sex-specific mechanisms and search for personalized treatment interventions for men and women with AUD.

References

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